

Amendments to the Claims

Please amend the claims as follows:

1 – 2. (Cancelled)

3. (Currently amended) The immunogenic composition of claim 120[[1]] ~~which wherein~~ said immunogenic composition is a subunit composition.

4. (Currently amended) The immunogenic composition of claim 3 wherein the at least one Neisserial autotransporter antigen comprises the passenger domain of Hsf, the at least one Neisserial Fe acquisition protein antigen is selected from the group consisting of TbpB high, TbpB low, and LbpB, Lipo28, and NMB0964, and the at least one different antigen is selected from the following list: FhaB, NspA, passenger domain of Hap, surface exposed domain of OMP85, FrpA, FrpC, ~~TbpB, LbpB~~, PldA, PilC, Lipo28, ~~and either or both of~~ LPS immunotype L2, and LPS immunotype L3.

5. (Currently amended) The immunogenic composition of claim 120[[1]] comprising an outer membrane vesicle preparation, wherein the antigens have been upregulated in the outer membrane vesicle.

6. (Currently amended) The immunogenic composition of claim 5 wherein the at least one Neisserial autotransporter antigen ~~is comprises~~ Hsf, the at least one Neisserial Fe acquisition protein antigen is selected from the group consisting of HpuA, HpuB, TbpA (high), TbpA (low), LbpA, LbpB, Lipo 28, NMB0964, and the at least one different antigen is selected from the following list: NadA, NspA, Hap, OMP85, HpuA, HpuB, TspA, TspB, FhaC, TbpA (high), TbpA (low), LbpA, TbpB, LbpB, PilQ, NM-ADPRT, P2086, TdfH, PorB, MafA, MafB, HimD, HisD, GNA1870, OstA, HlpA, MltA and PldA[;], ~~and optionally comprising either or both of~~ LPS immunotype L2, and LPS immunotype L3.

7. (Currently amended) The immunogenic composition of claim 120[[1]] comprising a subunit composition having one or more of the antigens, and an outer membrane vesicle preparation having at least one antigen which has been upregulated in the outer membrane vesicle.

8. (Cancelled)

9. (Previously presented) The immunogenic composition of claim 5 comprising at least two different outer membrane vesicle preparations.

10. (Original) The immunogenic composition of claim 9 wherein one outer membrane vesicle preparation is immunotype L2 and one outer membrane vesicle preparation is immunotype L3.

11. (Currently amended) The immunogenic composition of claim 120[[1]] wherein the at least one Neisserial autotransporter antigen is ~~comprises~~ Hsf and the at least one Neisserial Fe acquisition protein-different antigen is ~~comprises~~ TbpA (high).

12. (Canceled)

13. (Currently amended) The immunogenic composition of claim 11 wherein the at least one different antigen is ~~further comprising one or more additional antigens selected from the group a list consisting of Hap, LbpB, OMP 85 and FrpA.~~

14 – 16. (Cancelled)

17. (Currently amended) The immunogenic composition of claim 117[[1]] wherein the ~~comprising at least one Neisserial autotransporter antigen is~~ selected from the group consisting of Hsf, Hap, IgA protease, AspA and NadA;
the at least one Neisserial adhesin is NspA; and
at least one different further antigen is selected from the group consisting of : FhaB, PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, LbpB, FrpA, FrpC, FrpA/C, OMP85, PldA, LbpA, TbpA (low), TbpA(high), TbpB(low), TbpB(high), HpuA, HpuB, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD, and ~~either or both of~~ LPS immunotype L2, and LPS immunotype L3.

18 – 19. (Cancelled)

20. (Currently amended) The immunogenic composition of claim 120[[1]] wherein the ~~comprising~~ at least one Neisserial autotransporter antigen is selected from the group consisting of Hsf, Hap, IgA protease, AspA and NadA;
the at least one Neisserial Fe acquisition protein is selected from TbpA (high), Lipo28, and NMB0964; and
at least one different ~~further~~ antigen is selected from the group consisting of: FhaB, PilC, MafA, MafB, Omp26, NMB0995, FhaC, ~~FbpA, Bcp,~~ NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, ~~LbpB,~~ FrpA, FrpC, FrpA/C, OMP85, PldA, LbpA, TbpA(low), ~~TbpB(low), TbpB(high), HpuA, HpuB,~~ PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, NspA, TspA, TspB, P2086, ~~Lipo28, Sibp, NMB0964, NMB0293, NMB0315,~~ NMB1119, TdfH, PorB, NM-ADPRT, VapD, ~~and either or both of~~ LPS immunotype L2, and LPS immunotype L3.

21. (Cancelled)

22. (Currently amended) The immunogenic composition of claim 123[[1]] wherein the ~~comprising~~ at least one Neisserial autotransporter antigen is selected from the group consisting of Hsf, Hap, IgA protease, AspA and NadA;
the at least one Neisserial membrane associate protein is OMP85 or GNA1870; and
the at least one different ~~further~~ antigen is selected from the group consisting of: FhaB, PilC, MafA, MafB, Omp26, NMB0995, FhaC, ~~FbpA, Bcp,~~ NMB 1124, ~~NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, LpbB,~~ FrpA, FrpC, FrpA/C, PldA, ~~LbpA, TbpA(low), TbpA(high),~~ ~~[[-]] TbpB(low), TbpB(high), HpuA, HpuB, PilQ, MltA, HimD, HisD, GNA1870,~~ OstA, HlpA, NspA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, ~~TdfH, PorB, NM-ADPRT, VapD,~~ ~~and either or both of~~ LPS immunotype L2, and LPS immunotype L3.

23 – 44. (Cancelled)

45. (Currently amended) The immunogenic composition of claim 5 wherein a host cell from which the outer membrane vesicle preparation is derived has been engineered so as to down-regulate the expression of from one or more of lgtB or lgtE.

46 – 49. (Cancelled)

50. (Previously presented) The immunogenic composition of claim 5 wherein the outer membrane vesicle preparation contains LPS which is conjugated to an outer membrane protein (OMP).

51. (Previously presented) The immunogenic composition of claim 50 wherein LPS is conjugated to OMP in situ in the outer membrane vesicle preparation.

52. (Currently amended) The immunogenic composition of claim 120[[1]] comprising an antigen derived from *Neisseria meningitidis*.

53. (Cancelled)

54. (Currently amended) The immunogenic composition of claim 120[[1]] wherein all neisserial antigens are derived from *N.meningitidis*~~*N.meningitidis*~~.

55. (Currently amended) The immunogenic composition of claim 120[[1]] further comprising one or more bacterial capsular polysaccharides or oligosaccharides.

56. (Original) The immunogenic composition of claim 55 wherein the capsular polysaccharides or oligosaccharides are derived from bacteria selected from the group consisting of: *Neisseria meningitidis* serogroup A, C, Y and W-135, *Haemophilus influenzae* b, *Streptococcus pneumoniae*, Group A Streptococci, Group B Streptococci, *Staphylococcus aureus* and *Staphylococcus epidermidis*.

57. (Previously presented) The immunogenic composition of claim 55 wherein the capsular polysaccharide or oligosaccharide is conjugated to a protein.

58. (Currently amended) The immunogenic composition of claim 120[[1]] comprising an adjuvant.

59. (Previously presented) The immunogenic composition of claim 58 comprising aluminium salts.

60. (Previously presented) The immunogenic composition of claim 58 comprising 3D-MPL.

61. (Currently amended) A vaccine comprising the immunogenic composition of claim 120[[1]] and a pharmaceutically acceptable carrier.

62. (Cancelled)

63. (Withdrawn) A method for treatment or prevention of Neisserial disease comprising administering a protective dose of the vaccine of claim 61 to a host in need thereof.

64. (Withdrawn) The method of claim 63 in which *Neisseria meningitidis* infection is prevented or treated.

65. (Withdrawn) The method of claim 63 in which *Neisseria gonorrhoeae* infection is prevented or treated.

66 – 68. (Cancelled)

69. (Withdrawn) A genetically engineered Neisserial strain from which the outer membrane vesicle preparation of claim 5 is derived.

70. (Withdrawn) A method of making the immunogenic composition of claim 1 comprising a step of mixing together at least two antigens from Neisseria.

71. (Withdrawn) A method of making the immunogenic composition of claim 5 comprising a step of isolating outer membrane vesicles from a Neisserial culture.

72. (Withdrawn) The method of claim 71 comprising a further step of combining at least two outer membrane vesicle preparations.

73. (Withdrawn) The method of claim 72 wherein at least one outer membrane vesicle preparation contains LPS of immunotype L2 and at least one outer membrane vesicle preparation contains LPS of immunotype L3.

74. (Withdrawn) The method of claim 71 wherein the outer membrane vesicles are isolated by extracting with a concentration of DOC of 0 - 0.5%.

75. (Withdrawn) The method of claim 74 wherein the outer membrane vesicles are isolated by extracting with a concentration of DOC of 0.02%-0.4%, 0.04%-0.3%, 0.06%-0.2%, 0.08%-0.15% .

76. (Withdrawn) A method of making the vaccine of claim 61 comprising a step of combining the immunogenic composition with a pharmaceutically acceptable carrier.

77. (Withdrawn) A method of preparing an immune globulin for use in prevention or treatment of Neisserial infection comprising the steps of immunising a recipient with the vaccine of claim 61 and isolating immune globulin from the recipient.

78. (Withdrawn) An immune globulin prepared by the method of claim 77.

79. (Withdrawn) A pharmaceutical composition comprising the immune globulin of claim 78 and a pharmaceutically acceptable carrier.

80. (Withdrawn) A method for treatment or prevention of Neisserial infection comprising a step of administering to a patient an effective amount of the pharmaceutical preparation of claim 79.

81. (Cancelled)

82. (Previously presented) The immunogenic composition of claim 5, comprising a meningococcal bleb of immunotype L2 and a meningococcal bleb of immunotype L3.

83. (Original) The immunogenic composition of claim 82 wherein TbpA(high) is upregulated in one of the blebs.

84. (Cancelled)

85. (Previously presented) The immunogenic composition of claim 82 wherein Hsf is upregulated in one of the blebs.

86. (Previously presented) The immunogenic composition of claim 82 wherein OMP85 is upregulated in one of the blebs.

87. (Previously presented) The immunogenic composition of claim 82 wherein the blebs are isolated from meningococcal strains incapable of making capsular polysaccharide.

88. (Previously presented) The immunogenic composition of claim 82 wherein the L2 and/or L3 LPS oligosaccharide structures are truncated consistent with the blebs having been isolated from meningococcal strains that are lgtB⁻.

89. (Withdrawn) The immunogenic composition of claim 82 wherein the blebs are isolated from meningococcal strains that have downregulated expression of msbB.

90. (Previously presented) The immunogenic composition of claim 82 wherein the L2 and/or L3 LPS oligosaccharide moieties are intra-bleb conjugated to outer-membrane proteins integral to the bleb.

91 – 94. (Cancelled)

95. (Currently amended) The immunogenic composition of claim 17 wherein at least one Neisserial autotransporter antigen is comprising Hsf[[:]].

~~NspA; and~~

~~at least one further antigen selected from the group consisting of : FhaB, PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB~~

~~1313, NMB 1953, HtrA, Hsf, LbpB, FrpA, FrpC, FrpA/C, NadA, OMP85, PldA, LbpA, TbpA (low), TbpA (high), TbpB (low), TbpB (high), HpuA, HpuB, Hap, IgA protease, AspA, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.~~

96. (Currently amended) The immunogenic composition of claim 20 wherein at least one Neisserial autotransporter antigen is comprising

~~Hsf[[:]].~~

~~TbpA (high); and~~

~~at least one further antigen selected from the group consisting of: FhaB, PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, LbpB, FrpA, FrpC, FrpA/C, OMP85, PldA, LbpA, TbpB (low), TbpB (high), HpuA, HpuB, Hap, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, NspA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.~~

97. (Cancelled)

98. (Currently amended) The immunogenic composition of claim 22 wherein at least one Neisserial autotransporter antigen is comprising

~~Hsf[[:]].~~

~~OMP85; and~~

~~at least one further antigen selected from the group consisting of: FhaB, PilC, MafA, MafB, Omp26, NMB0995, FhaC, FbpA, Bcp, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA, LpbB, FrpA, FrpC, FrpA/C, PldA, LbpA, TbpA (high), TbpB (low), TbpB (high), HpuA, HpuB, Hap, PilQ, MltA, HimD, HisD, GNA1870, OstA, HlpA, NspA, TspA, TspB, P2086, Lipo28, Sibp, NMB0964, NMB0293, NMB0315, NMB1119, TdfH, PorB, NM-ADPRT, VapD and either or both of LPS immunotype L2 and LPS immunotype L3.~~

99 – 113. (Cancelled)

114. (Previously presented) The immunogenic composition of Claim 5 wherein the antigens have been upregulated in the outer membrane vesicle by growth of a parental strain of *Neisseria* under iron limitation conditions.

115. (Previously presented) The immunogenic composition of Claim 7 wherein the at least one antigen upregulated in the outer membrane vesicle has been upregulated by growth of a parental strain of *Neisseria* under iron limitation conditions.

116. (New) An immunogenic composition comprising at least one *Neisseria* autotransporter antigen, at least one *Neisseria* adhesin antigen, and at least one different antigen, wherein each of said antigens is isolated or enriched, and wherein the at least one different antigen is selected from the following categories:

- a) *Neisseria* toxin antigens;
- b) *Neisseria* Fe acquisition protein antigens; and
- c) *Neisseria* membrane associated protein antigens.

117. (New) The immunogenic composition of claim 116, wherein the at least one *Neisseria* autotransporter antigen is selected from the group consisting of Hsf, Hap, IgA protease, AspA and NadA; the at least one *Neisseria* adhesin antigen is selected from the group consisting of FhaB, NspA, PilC, Hsf, Hap, MafA, MafB, Omp26, NMB0315, NMB0995, NMB1119 and NadA; and the at least one different antigen is selected from the group consisting of:

- a) *Neisseria* toxins FrpA, FrpC, FrpA/C, VapD, NM-ADPRT, lipopolysaccharide (LPS) immunotype L2, and LPS immunotype L3;
- b) *Neisseria* Fe acquisition proteins TbpA high, TbpA low, TbpB high, TbpB low, LbpA, LbpB, P2086, HpuA, HpuB, Lipo28, Sibp, FbpA, BfrA, BfrB, Bcp, NMB0964 and NMB0293; and
- c) *Neisseria* membrane associated proteins PilQ, OMP85, FhaC, NspA, TbpA(high), TbpA(low), LbpA, HpuB, TspA, TspB, TdfH, PorB, HimD, HisD, GNA1870, OstA, HlpA, MitA, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA and PldA.

118. (New) The immunogenic composition of claim 117, wherein each of the at least one Neisserial autotransporter antigen, the at least one Neisserial adhesin antigen, and the at least one different antigen are isolated.

119. (New) An immunogenic composition comprising at least one Neisserial autotransporter antigen, at least one Neisserial Fe acquisition protein antigen, and at least one different antigen, wherein each of said antigens is isolated or enriched, and wherein the at least one different antigen is selected from the following categories:

- a) Neisserial toxin antigens;
- b) Neisserial adhesin antigens; and
- c) Neisserial membrane associated protein antigens.

120. (New) The immunogenic composition of claim 119, wherein the at least one Neisserial autotransporter antigen is selected from the group consisting of Hsf, Hap, IgA protease, AspA and NadA; the at least one Neisserial Fe acquisition protein antigen selected from the group consisting of TbpA high, TbpA low, TbpB high, TbpB low, LbpA, LbpB, P2086, HpuA, HpuB, Lipo28, Sibp, FbpA, BfrA, BfrB, Bcp, NMB0964 and NMB0293; and the at least one different antigen is selected from the group consisting of:

- a) Neisserial toxins FrpA, FrpC, FrpA/C, VapD, NM-ADPRT, lipopolysaccharide (LPS) immunotype L2, and LPS immunotype L3;
- b) Neisserial adhesins selected FhaB, NspA, PilC, Hsf, Hap, MafA, MafB, Omp26, NMB0315, NMB0995, NMB1119 and NadA; and
- c) Neisserial membrane associated proteins-selected PilQ, OMP85, FhaC, NspA, TbpA(high), TbpA(low), LbpA, HpuB, TspA, TspB, TdfH, PorB, HimD, HisD, GNA1870, OstA, HlpA, MltA, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA and PldA.

121. (New) The immuogenic composition of claim 120, wherein each of the at least one Neisserial autotransporter antigen, the at least one Neisserial adhesin antigen, and the at least one different antigen are isolated.

122. (New) An immunogenic composition comprising at least one Neisserial autotransporter antigen, at least one Neisserial membrane associated protein, and at least one different antigen, wherein each of said antigens is isolated or enriched, and wherein the at least one different antigen is selected from the following categories:

- a) Neisserial toxin antigens;
- b) Neisserial adhesin antigens; and
- c) Neisserial Fe acquisition protein antigens.

123. (New) The immunogenic composition of claim 122, wherein the at least one Neisserial autotransporter antigen is selected from the group consisting of Hsf, Hap, IgA protease, AspA and NadA and NMB0293; the at least one Neisserial membrane associated protein-selected from the group consisting of PilQ, OMP85, FhaC, NspA, TbpA(high), TbpA(low), LbpA, HpuB, TspA, TspB, TdfH, PorB, HimD, HisD, GNA1870, OstA, HlpA, MltA, NMB 1124, NMB 1162, NMB 1220, NMB 1313, NMB 1953, HtrA and PldA, and the at least one different antigen is selected from the group consisting of:

- a) Neisserial toxins FrpA, FrpC, FrpA/C, VapD, NM-ADPRT, lipopolysaccharide (LPS) immunotype L2, and LPS immunotype L3;
- b) Neisserial adhesins FhaB, NspA, PilC, Hsf, Hap, MafA, MafB, Omp26, NMB0315, NMB0995, NMB1119 and NadA; and
- c) Neisserial Fe acquisition proteins antigen selected from the group consisting of TbpA high, TbpA low, TbpB high, TbpB low, LbpA, LbpB, P2086, HpuA, HpuB, Lipo28, Sibp, FbpA, BfrA, BfrB, Bcp, NMB0964.

124. (New) The immuogenic composition of claim 123, wherein each of the at least one Neisserial autotransporter antigen, the at least one Neisserial adhesin antigen, and the at least one different antigen are isolated.

125. (New) The immunogenic composition of claim 117 wherein the at least one Neisserial autotransporter antigen is Hsf and the at least one Neisserial Fe adhesin antigen is Hap.

126. (New) The immunogenic composition of claim 117 further comprising an adjuvant.

127. (New) A vaccine comprising the immunogenic composition of claim 117 and a pharmaceutically acceptable carrier.

128. (New) The immunogenic composition of claim 117, wherein said immunogenic composition is a subunit composition.

129. (New) The immunogenic composition of claim 123 wherein the at least one Neisserial autotransporter antigen is Hsf and the at least one Neisserial Fe membrane-associated protein is OMP85 or GNA1870.

130. (New) The immunogenic composition of claim 123 further comprising an adjuvant.

131. (New) A vaccine comprising the immunogenic composition of claim 123 and a pharmaceutically acceptable carrier.

132. (New) The immunogenic composition of claim 123, wherein said immunogenic composition is a subunit composition.